

- 92 -

CLAIMS:

1. A method of modulating the inflammatory response in a mammal, said method comprising modulating the functional activity of activin wherein upregulating activin or
5 fragments, derivatives, mutants or variants thereof to a functionally effective level in said mammal induces, maintains or upregulates the pro-inflammatory mediator cascade and downregulating activin to a functionally ineffective level in said mammal inhibits or retards the pro-inflammatory mediator cascade.
- 10 2. A method of therapeutically and/or prophylactically treating a condition, or a predisposition to the development of a condition, characterised by an aberrant, unwanted or otherwise inappropriate inflammatory response in a mammal, said method comprising modulating the level of activin or fragments, derivatives, mutants or variants thereof in
15 said mammal where upregulating activin to a functionally effective level upregulates the pro-inflammatory mediator cascade and downregulating activin to a functionally ineffective level inhibits or retards the pro-inflammatory mediator cascade.
3. The method according to claim 1 or 2 wherein said activin is activin A or an activin molecule comprising the β_B subunit or fragment, derivative, mutant or variant thereof.
20
4. The method according to claim 3 wherein said molecule comprising the β_B subunit is activin B.
5. The method according to claim 3 or 4 wherein said inflammatory response is a
25 local inflammatory response.
6. The method according to claim 5 wherein said local inflammatory response occurs in the context of airway inflammation, rheumatoid arthritis, inflammatory bowel disease, pancreatitis, atherosclerosis, meningitis, appendicitis, angiogenesis, psoriasis, neural
30 protection, renal tubular necrosis, allergic responses, rheumatoid arthritis, encephalitis, multiple sclerosis, traumatic brain injury, and wound healing.

- 93 -

7. The method according to claim 6 wherein said airway inflammation is asthma, interstitial lung disease, cystic fibrosis, lung transplantation, bronchiolitis obliterans, emphysema, obstructive pulmonary disease, severe acute respiratory syndrome, asbestosis, obstructive sleep apnoea, hypoxia or pulmonary hypertension.
8. The method according to claim 6 wherein said wound healing is associated with surgery or burns.
9. The method according to claim 3 or 4 wherein said inflammatory response is a systemic inflammatory response.
10. The method according to any one of claims 5 to 9 wherein said inflammatory response is acute.
11. The method according to claim 10 wherein said acute inflammatory response is associated with septic shock, septicaemia, airway inflammation, appendicitis, meningitis, hepatic response to toxins or viruses, angiogenesis, psoriasis, neural protection, atherosclerosis, renal tubular necrosis, wound healing or traumatic injury.
12. The method according to claim 11 wherein said airway inflammation occurs in the context of asthma, interstitial lung disease, cystic fibrosis, lung transplantation, bronchiolitis obliterans, emphysema, obstructive pulmonary disease, severe acute respiratory syndrome, asbestosis, obstructive sleep apnoea, hypoxia or pulmonary hypertension.
13. The method according to claim 10 wherein said acute systemic inflammatory response occurs in the context of systemic inflammatory response syndrome.
14. The method according to claim 13 wherein said systemic inflammatory response syndrome is sepsis, septicaemia, toxic shock, septic shock, tissue trauma, meningitis or

- 94 -

appendicitis.

15. The method according to claim 3 or 5 wherein said inflammatory response is a chronic response.

5

16. The method according to claim 15 wherein said chronic inflammatory response is multiple sclerosis, inflammatory bowel disease, rheumatoid arthritis, asthma, psoriasis or wound healing.

10 17. The method according to any one of claims 5-16 wherein said inflammatory response is an unwanted response and said modulation of the inflammatory response is downregulation of the inflammatory response.

15 18. The method according to claim 17 wherein said downregulation of the inflammatory response is achieved by downregulating the pro-inflammatory cytokine cascade.

19. The method according to claim 18 wherein said pro-inflammatory cytokine cascade corresponds to the expression of $\text{TNF}\alpha$, IL-1 and/or IL-6.

20

20. The method according to any one of claims 1-16 wherein said modulation is upregulation of activin functional activity and said upregulation is achieved by introducing into said mammal a nucleic acid molecule encoding activin or functional equivalent, derivative, or homologue thereof or the activin expression product or functional fragment,
25 derivative, mutant or variant thereof.

21. The method according to any one of claims 1-19 wherein said modulation is achieved by introducing into said mammal a proteinaceous or non-proteinaceous molecule which modulates transcriptional and/or translational regulation of the activin gene.

30

22. The method according to any one of claims 1-16 wherein said modulation is

- 95 -

upregulation of activin functional activity and said upregulation is achieved by introducing into said mammal a proteinaceous or non-proteinaceous molecule which functions as an agonist of the activin expression product.

5 23. The method according to any one of claims 1-19 wherein said modulation is downregulation of activin functional activity and said downregulation is achieved by introducing into said mammal a proteinaceous or non-proteinaceous molecule which functions as an antagonist to the activin expression product.

10 24. The method according to any one of claims 20-23 wherein said activin is activin A or an activin molecule comprising the β_B subunit or fragment, derivative, mutant or variant thereof.

15 25. The method according to claim 24 wherein said molecule comprising the β_B subunit is activin B.

20 26. The method according to claim 23 wherein said antagonist is follistatin or functional fragments, derivative, homologue or mimetic thereof, an agent that upregulates the levels of the α subunit of inhibin, inhibin, an agent that upregulates the levels of β_C , an activin neutralising antibody or an activin mutant.

27. The method according to claim 23 wherein said antagonist is an anti-activin antibody.

25 28. The method according to claim 27 wherein said antibody is directed to the β_A subunit of activin.

29. The method according to claim 27 wherein said antibody is directed to the β_B subunit of activin.

30 30. The method according to any one of claims 1-29 wherein said mammal is a human.

- 96 -

31. Use of an agent capable of modulating the functionally effective level of activin in the manufacture of a medicament for the therapeutic and/or prophylactic treatment of a condition, or a predisposition to the development of a condition, characterised by an aberrant, unwanted or otherwise inappropriate inflammatory response in a mammal wherein upregulating activin to a functionally effective level upregulates the pro-inflammatory mediator cascade and downregulating activin to a functionally ineffective level inhibits or retards the pro-inflammatory mediator cascade.
32. Use according to claim 31 wherein said activin is activin A or an activin molecule comprising the β_B subunit or fragment, derivative, mutant or variant thereof.
33. Use according to claim 32 wherein said molecule comprising the β_B subunit is activin B.
34. Use according to claim 32 or 33 wherein said inflammatory response is a local inflammatory response.
35. Use according to claim 34 wherein said local inflammatory response occurs in the context of airway inflammation, rheumatoid arthritis, inflammatory bowel disease, pancreatitis, atherosclerosis, meningitis, appendicitis, angiogenesis, psoriasis, neural protection, renal tubular necrosis, allergic responses, encephalitis, rheumatoid arthritis, multiple sclerosis, traumatic brain injury, and wound healing.
36. Use according to claim 35 wherein said airway inflammation is asthma, interstitial lung disease, cystic fibrosis, lung transplantation, bronchiolitis obliterans, emphysema, obstructive pulmonary disease, severe acute respiratory syndrome, asbestosis, obstructive sleep apnoea, hypoxia or pulmonary hypertension.
37. Use according to claim 35 wherein said wound healing is associated with surgery or burns.

- 97 -

38. Use according to claim 32 or 33 wherein said inflammatory response is a systemic inflammatory response.

5 39. Use according to any one of claims 34-38 wherein said inflammatory response is acute.

40. Use according to claim 39 wherein said acute inflammatory response is associated with septic shock, septicaemia, airway inflammation, appendicitis, meningitis, hepatic
10 response to toxins or viruses, angiogenesis, psoriasis, neural protection, atherosclerosis, renal tubular necrosis, wound healing or traumatic injury.

41. Use according to claim 40 wherein said airway inflammation occurs in the context of asthma, interstitial lung disease, cystic fibrosis, lung transplantation, severe acute
15 respiratory syndrome, bronchiolitis obliterans, emphysema, obstructive pulmonary disease, asbestosis, obstructive sleep apnoea, hypoxia or pulmonary hypertension.

42. Use according to claim 39 wherein said acute systemic inflammatory response occurs in the context of systemic inflammatory response syndrome.

20 43. Use according to claim 42 wherein said systemic inflammatory response syndrome is sepsis, septicaemia, toxic shock, septic shock, tissue trauma, meningitis or appendicitis.

44. Use according to claim 32 or 33 wherein said inflammatory response is a chronic
25 response.

45. Use according to claim 44 wherein said chronic inflammatory response is multiple sclerosis, inflammatory bowel disease, rheumatoid arthritis, asthma, psoriasis or wound
30 healing.

46. Use according to any one of claims 34-43 wherein said inflammatory response is an

- 98 -

unwanted response and said modulation of the inflammatory response is downregulation of the inflammatory response.

47. Use according to claim 46 wherein said downregulation of the inflammatory
5 response is achieved by downregulating the pro-inflammatory cytokine cascade.

48. Use according to claim 47 wherein said pro-inflammatory cytokine cascade corresponds to the expression of $\text{TNF}\alpha$, IL-1 and/or IL-6.

10 49. Use according to any one of claims 31-43 wherein said modulation is upregulation of activin functional activity and said upregulation is achieved by introducing into said mammal a nucleic acid molecule encoding activin or functional equivalent, derivative, or homologue thereof or the activin expression product or functional fragment, derivative, mutant or variant thereof.

15 50. Use according to any one of claims 31-43 wherein said modulation is achieved by introducing into said mammal a proteinaceous or non-proteinaceous molecule which modulates transcriptional and/or translational regulation of the activin gene.

20 51. Use according to any one of claims 31-43 wherein said modulation is upregulation of activin functional activity and said upregulation is achieved by introducing into said mammal a proteinaceous or non-proteinaceous molecule which functions as an agonist of the activin expression product.

25 52. Use according to any one of claims 31-43 wherein said modulation is downregulation of activin functional activity and said downregulation is achieved by introducing into said mammal a proteinaceous or non-proteinaceous molecule which functions as an antagonist to the activin expression product.

30 53. Use according to any one of claims 49-52 wherein said activin is activin A or an activin molecule comprising the β_B subunit or fragment, derivative, mutant or variant

- 99 -

thereof.

54. Use according to claim 53 wherein said molecule comprising the β_B subunit is activin B.

5

55. Use according to claim 52 wherein said antagonist is follistatin or functional fragments, derivative, homologue or mimetic thereof, an agent that upregulates the levels of the α subunit of inhibin, inhibin, an agent that upregulates the levels of β_C , an activin neutralising antibody or an activin mutant.

10

56. Use according to claim 52 wherein said antagonist is an anti-activin antibody.

57. Use according to claim 56 wherein said antibody is directed to the β_A subunit of activin.

15

58. Use according to claim 56 wherein said antibody is directed to the β_B subunit of activin.

59. Use according to any one of claims 31-43 wherein said mammal is a human.

20

60. A pharmaceutical composition comprising the modulatory agent as hereinbefore defined and one or more pharmaceutically acceptable carriers and/or diluents when used in the method of any one of claims 1-30.

25